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## EUROPEAN PATENT APPLICATION

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### Remarks:

A request for correction of description, claims and abstract has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 3.).

### (54) Oral composition for the treatment of halitosis

(57) Includes: a) chlorhexidin digluconate in a concentration by weight of 0.025 to 0.20% or other soluble and pharmaceutically acceptable chlorhexidin salt in an equivalent concentration of chlorhexidin base; b) cetyl pyridinium chloride or other pharmaceutically acceptable salt of quaternary ammonium in a concentration by weight of 0.025 to 0.10%; c) a pharmaceutically accept-

able salt or compound of Zn(+2) and/or Cu(+2) which includes from 100 to 1,000 ppm of Zn(+2) and/or Cu(+2) ions.

The present invention also relates to the use of said composition for obtaining a mouth rinse, a dental paste, a dental powder or dental chewing gum for the treatment of oral halitosis.

**Description****FIELD OF THE INVENTION**

5 [0001] The present invention relates to a stable oral composition permitting total bioavailability of active ingredients of considerable anti-plaque effect with low staining of the teeth for the treatment of oral halitosis.  
 [0002] The invention also relates to the use of said composition in the form of mouth rinses, dentifrices and the like for the treatment of oral halitosis.

**10 BACKGROUND OF THE INVENTION**

[0003] Halitosis is the term used to describe bad breath emitted by the mouth, independently of whether the bad-smelling substances are of oral origin or non-oral origin such as the respiratory or digestive tracts.  
 [0004] The etiology and pathogenesis of oral halitosis is based on local buccal factors which lead to high microbial metabolism in alkaline medium. This causes the emission of volatile sulphurous compounds (VSC) responsible for the bad breath, most of which have their origin in the breakdown of sulphur-rich hydrolysed amino acids by anaerobic gram-negative bacteria in an alkaline medium.  
 [0005] The problems of oral halitosis often accompany and can be the manifestation of pathologies of the oral cavity caused, for example, by excessive accumulation of bacterial plaque. Under this aspect there are numerous references to dental compositions with bactericidal and anti-plaque activity.  
 [0006] Patent US-4,022,880 describes the anti-plaque effect provided by combination of Zn salts with an antibacterial agent such as chlorhexidin.  
 [0007] However, prolonged utilisation of chlorhexidin digluconate at concentrations higher than 0.20% leads to staining of the teeth and loss of sense of taste. The chlorhexidin presents sustained activity over the course of time.  
 [0008] Furthermore, patent US-4,647,452 relates to an oral composition of improved efficacy against dental plaque. Said oral composition comprises zinc salts with salicylamides of specific structure for use thereof in the inhibition of dental plaque.  
 [0009] Patent EP 0546627-A1 describes a stable oral anti-plaque composition which contains zinc salts and Triclosan in a wetting agent system. The object of said patent is to provide a stable oral composition with marked anti-plaque activity by combining an anti-plaque system resulting from a mixture of zinc salts with Triclosan, with a wetting agent system resulting from the combination of a high water content with a certain type of surface-active agents.  
 [0010] Patent US-5,236,699 describes an anti-plaque mouth-rinse composition which includes Triclosan (5-chloro-2-(2,4-dichlorophenoxy)-phenol and cetyl piridinium chloride which when used separately are of limited efficacy but, when combined, increase the antibacterial activity, thereby inhibiting the formation of dental plaque. Triclosan alone, however, does not show a long effect over time, due its low substantivity [Gilbert 1987], while its anti-plaque activity is lower than that of chlorhexidin [Jekins, Addy and Newcombe, J. Clin. Periodontol., 1994;21:250-255].  
 [0011] Also forming part of the state of the art is the disclosure of international patent WO 92/13514. Said patent relates to oral compositions for buccal hygiene which include bromochlorophene and zinc ions in a ratio by weight between 1:0.1 and 1:50. The combination of these components provides a synergistic anti-plaque effect.  
 [0012] Also increasingly evident among the aforesaid problems related with teeth care are those involving bad breath from the mouth. Patent EP 0436284-A1 discloses a stable oral composition which includes a zinc compound for the control of bad breath and prevention of calculus.  
 [0013] Patents U.S. 2,894,876 and U.S. 5,211,940 also mention the use of certain Cu(+2) salts in preparations for oral use in attempting to combat bad breath.  
 [0014] The effect of the metallic ions Zn(+2) and/or Cu(+2), when used alone and without any other active ingredient, is relatively limited and does not permit highly efficacious treatment of the problem of halitosis.  
 [0015] Therefore, there does not yet exist in the state of the art a stable composition which presents high anti-plaque effect, low staining of the teeth, total bioavailability of the active ingredients, while also presenting marked anti-halitosis activity.

**50 DESCRIPTION OF THE INVENTION**

[0016] The composition of the present invention manages to overcome the problems of the prior art, while also providing other advantages which will be described below.  
 [0017] The present invention relates to a stable oral composition of high anti-plaque effect, low staining of the teeth, total bioavailability of the active ingredients and marked antihalitosis activity.  
 [0018] The authors of the present invention have found, surprisingly, that a certain combination of three compounds, two antiseptic agents at very low doses and a salt or compound of Zn(+2) and/or Cu(+2), has an anti-plaque effect and

anti-halitosis activity greater than that which could be obtained from the components used separately.

[0019] The composition of the present invention includes chlorhexidin digluconate in a concentration by weight of 0.025 to 0.20% or other chlorhexidin salt in an equivalent concentration of chlorhexidin base, cetyl pyridinium chloride or other salt of quaternary ammonium in a concentration by weight of 0.025 to 0.10% and a pharmaceutically acceptable salt or compound of Zn(+2) and/or Cu(+2) which includes from 100 to 1,000 ppm of Zn(+2) and/or Cu(+2) ions.

[0020] The composition of the present invention does not affect the composition of the bacterial flora present in the mouth cavity, and provides high anti-plaque effect with low staining of the teeth.

[0021] The composition of the invention provides a product with marked anti-halitosis activity, for daily use and without negative effects due to the low concentration of the active ingredients present in same.

[0022] There follows a brief description of the characteristics of each one of the components used in the composition of the present invention.

[0023] On the one hand, chlorhexidin digluconate [1,6-di-(N-p-chlorophenyl diguanide) hexane-digluconate] is a biguanidic by-product with a cationic charge. It is a bactericidal and anti-plaque agent of high substantivity to the structures of the mouth cavity (teeth enamel, mucous membranes, etc.). It is effective against a broad spectrum of gram-positive and gram-negative bacteria. E1 chlorhexidin gluconate has water solubility exceeding 50% by weight, with weakly acid reaction and precipitates in alkaline medium. Chlorhexidin has the property of preventing bacterial adhesion, interrupting the formation of bacterial masses, maintaining an anti-microbial state of activity and retaining its effect over a long period of time (substantivity).

[0024] Furthermore, the quaternary ammonium salts usually present intense bactericidal activity, though of shorter duration than that of chlorhexidin. The CPC in particular presents detergent and antiseptic activity, though the presence of proteins, serum, lipids and phospholipids reduces said activity.

[0025] The free Zn(+2) and Cu(+2) ions show that they possess great capacity for forming insoluble salts with nucleophilic compounds such as valeric acid, hydrogen sulphide, mercaptans and the like. These compounds are the anaerobic by-products of the gram-negative bacteria and the ones chiefly responsible for bad breath.

[0026] In the comparative examples which will be described below, in the examples section, the surprising effect of the oral composition of the present invention can be observed.

[0027] The composition of the invention further includes a wetting agent selected from among glycerine, sorbitol 70%, PEG-400 and PEG-600, propylene glycol or the like in a concentration by weight of 5-15%. The wetting agent is added for a triple purpose: to lend "body" to a composition which would otherwise be of very low viscosity, to eliminate the possibility of crystallisation and, finally, to add a complementary sweetening effect different from that imparted by the saccharine.

[0028] The composition also includes a non-ionic or amphoteric surface-active agent selected from among polyoxyethylene esters (sorbitan-monoisostearate, monoisooleate, monolaurate), copolymers in block of poly (oxypropylene)-poly(oxyethylene), polyhydroxypropyl esters, PEG-40 hydrogenated ricin oil, PEG-60 hydrogenated ricin oil, propyl betaine cocamide and the like in a concentration by weight of 0.2-0.8%. The surface-active agent is also added with a double purpose: on the one hand, to solubilize the essences present, since they are oily in character and, on the other hand, to lend a certain foaming capacity to the composition and thereby facilitate the suspension and consequent elimination of impurities present in the mouth cavity.

[0029] It also includes fluorides selected from among sodium fluoride, cetyl-amine fluorhydrate, a derivative fluorinate of octadecylamine (DFO) or another pharmaceutically acceptable source of fluorine ions corresponding to a concentration in free fluorine ions of up to 2500 ppm. The fluorinated compounds are added to the composition in order to assist demineralisation of the teeth. The fluorides at low concentration mean that the hydroxylapatite  $\text{Ca}_5(\text{PO}_4)_3\text{OH}$  is converted into fluoroapatite  $\text{Ca}_5(\text{PO}_4)_3\text{F}$ , which is more resistant to acid attack. Moreover, the fluorides block, among other enzymes, the enzyme endolase which is responsible for conversion of the carbohydrates into acids.

[0030] The composition also includes a sweetener such as saccharine at a concentration by weight of 0.005-0.10% and/or xylitol at a concentration by weight of 2-10%, essences in a concentration by weight of 0.05-0.20 and a colorant in a concentration by weight of 0.0001 - 0.001%.

[0031] None of the additional components described above is essential for obtaining the surprising effect of the composition of the present invention, though the addition thereof does enhance the properties of the end product.

[0032] There follows an outline of the main advantages involved in utilisation of the composition of the present invention. The composition of the invention reduces the anaerobic gram-negative bacteria mainly responsible for the halitosis phenomenon. The products of decomposition are neutralised with immediate reduction of the bad breath and of the irritation which can be provoked by the volatile sulphurous compounds, VSC.

[0033] Furthermore, owing to the low concentration of antiseptics and especially of chlorhexidin, minimal or nil alteration of the oral flora is achieved, while staining of the teeth and loss of sense of taste is also avoided.

[0034] An anti-caries action is achieved when the composition includes the additional fluoride component described above. Furthermore, due to the very good substantivity of the active ingredients used, a prolonged action over time is achieved, which makes frequent applications unnecessary (maximum of twice daily).

[0035] Provided below are a number of non-restrictive examples of the scope of the invention, showing preferred embodiments of the composition of the invention. Possible variations which an expert in the subject might make in the components of the composition and considered equivalent to the elements described in the description of the invention will also be considered within the sphere of protection of the present invention.

[0036] Table A below shows seven compositions which include the different percentages and components described in the description of the invention.

Table A

Component	Comp. 1 (%)	Comp. 2 (%)	Comp. 3 (%)	Comp. 4 (%)	Comp. 5 (%)	Comp. 6 (%)	Comp. 7 (%)
Chlorhexidin digluconate (CHX)	0.05	0.025	0.05	0.05	0.05	0.075	0.075
Cetyl piridinium chloride (CPC)	0.05	0.025	0.05	0.05	0.05	0.05	0.05
Cu gluconate Zn gluconate Zn lactate Zn chloride Cu acetate	0.50	0.15	0.15	0.50	0.15	0.25	0.10
Saccharine	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Xylitol	5.0	5.0	10.0	5.0	5.0	10	10
Glycerine USP	5.0	10.0	10.0	5.0	5.0	10	10
Colorant	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
PEG-40 hydrogenated ricin oil or propyl betaine cocamide	0.60	0.60	0.60	0.60	0.80	0.60	0.60
Essence	0.15	0.10	0.15	0.15	0.20	0.15	0.15
Alcohol 96% or 2,4-dichlorobencil alcohol	5.0	0.10	1.0	5.0	-	-	-
Deionized water c. p.s.	100	100	100	100	100	100	100
pH	6.30	6.15	6.20	6.30	5.90	6.15	6.0

[0037] Composition 5 also includes a fluorinated by-product of octadecylamine (DFO) at a concentration of 0.80%, approximately equivalent to 200 ppm of fluorine ions.

[0038] Comparative examples have also been carried out showing the surprising effect of the composition of the present invention.

#### COMPARATIVE EXAMPLES

[0039] In vitro microbiological examples are provided below relating to the antibacterial activity on microorganisms involved in the problem of halitosis, both in respect of the individual active ingredients and the binary mixtures and the composition of the invention.

#### Example 1

[0040] The anti-microbial activity of a certain number of active ingredients was obtained by study of the minimum

inhibiting concentrations (MIC) of the respective agents (by the method of diffusion in agar) against bacteria representing periodontal disease.

[0041] The results of this evaluation are shown in Table 1 below.

TABLE 1

Agents	Antimicrobial activity (in %) against bacteria		
	<i>P.gingivalis</i>	<i>P.intermedia</i>	<i>A.actinomycetemcomitans</i>
Zn <sup>++</sup> , sulphate	0.5	0.5	0.1
Hexetidin	0.001	0.001	0.09
Chlorhexidin	0.002	0.0009	0.004
CPC	0.0006	0.0003	>0.02
Triclosan	0.004	0.009	0.0006
Cu <sup>++</sup> gluconate	0.06	0.004	NI*

\* Not inhibited

[0042] The data show the scant activity of zinc salts and the better activity of the rest of the active ingredients, notable among which is chlorhexidin due to its better results in general on the three bacteria.

#### Example 2

[0043] The presence or absence of activity in a certain number of binary mixtures active ingredients was determined by the method of diffusion in agar using discs impregnated in the respective mixtures, against major bacteria associated with periodontal disease.

[0044] The results are shown in Table 2 below.

TABLE 2

	Mixtures	Presence of anti-microbial activity in binary mixtures		
		<i>P.gingivalis</i>	<i>P.intermedia</i>	<i>A.actinomycetemcomitans</i>
1	Hexetidin + Chlorhexidin	+	+	-
2	Zn <sup>++</sup> Sulphate + chlorhexidin	+	+	+
3	CPC + Hexetidin	+	+	-
4	Zn <sup>++</sup> Sulphate + Hexetidin	+	+	+
5	Zn <sup>++</sup> Sulphate + CPC	+	+	+
6	CPC + Chlorhexidin	+	+	+

[0045] The results showed the appearance of strong antagonisms, of which mixtures 1 and 3 are an example, against *A. actinomycetemcomitans*. No notable antagonisms or synergies could be observed for the other cases from the diffusion haloes obtained.

[0046] The MICs of the binary mixtures selected were then obtained, as against each agent alone, in order to determine any possible increases in the anti-microbial efficacy of the mixtures.

[0047] The MIC readings shown in any case gave an MIC very similar to that of the most effective product for each bacterium, which led to the conclusion that there was possibly an "in vitro" potential additive effect of the substances studied.

#### Example 3

[0048] The anti-microbial activity of the mouth rinse evaluated "in vitro" by mortality studies over short intervals of time (short interval killing test, SIKT) against a mixture of periodontal bacteria containing between  $1.0 \cdot 10^5$  and  $1.0 \cdot 10^7$  UFC/ml of each stock. The total counts obtained in the surviving flora and those pertaining to each stock after one

minute of contact are summarised in Tables 3 and 4.

TABLA 3

Total UFC/ml recovered (%) at 1 minute	
PBS	100%
Composition of the inv.	0.05%
CHX	25.55%
Zn <sup>++</sup> , sulphate	47.65
CPC	0.04%

TABLE 4

	PBS	Composition of the inv.	CHX	Zn <sup>++</sup> , sulphate	CPC
<i>F. nucleatum</i>	100%	0.35	0.87	40.9	0.05
<i>P. gingivalis</i>	100%	<0.01	<0.81	33.9	<0.01
<i>P. intermedia</i>	100%	<0.01	<0.56	0.56	0.01
<i>Peptostreptococcus micros</i>	100%	0.06	82.12	54.5	0.03

[0049] From Table 3 it can be deduced that the initial effect of the composition of the invention against the total flora was similar to that of the CPC, which gave viable recovered percentages similar to those of the composition of the invention.

[0050] The conclusion that the principal anti-microbial activity of the composition of the invention is due only to the CPC is partly corrected thanks to the data of Table 4. The data shown in Table 4 show and confirm its activity on various bacteria, improved for *P. intermedia* by the presence of CHX and Zn<sup>++</sup>.

### Claims

1. Oral composition which includes a) chlorhexidin digluconate in a concentration by weight of 0.025 to 0.20% or other soluble and pharmaceutically acceptable chlorhexidin salt in an equivalent concentration of chlorhexidin base; b) cetyl pyridinium chloride or other pharmaceutically acceptable salt of quaternary ammonium in a concentration by weight of 0.025 to 0.10%; c) a pharmaceutically acceptable salt or compound of Zn(+2) and/or Cu(+2) which includes from 100 to 1,000 ppm of Zn(+2) and/or Cu(+2) ions.
2. Composition as claimed in Claim 1, which further includes a wetting agent selected from among glycerine, sorbitol 70%, PEG-400 and PEG-600, propylene glycol or the like in a concentration by weight of 5-15%.
3. Composition as claimed in Claims 1 or 2, which also includes a non-ionic or amphoteric surface-active agent selected from among polyoxyethylene esters (sorbitan-monoisostearate, monoisooleate, monolaurate), copolymers in block of poly(oxypropylene)-poly(oxyethylene), polyhydroxypropyl esters, PEG-40 hydrogenated ricin oil, PEG-60 hydrogenated ricin oil, propyl betaine cocamide and the like in a concentration by weight of 0.2-0.8%.
4. Composition as claimed in Claim 1, 2 or 3, which also includes fluorides selected from among sodium fluoride, cetyl-amine fluorhydrate, a derivative fluorinate of octadecylamine (DFO) or another pharmaceutically acceptable source of fluorine ions corresponding to a concentration in free fluorine ions of up to 2500 ppm.
5. Composition as claimed in any of the previous claims, which also includes a sweetener such as saccharine at a concentration by weight of 0.005-0.10% and/or xylitol at a concentration by weight of 2-10%.
6. Composition as claimed in any of the above claims, which also includes essences in a concentration by weight of 0.05-0.20 and a colorant in a concentration by weight of 0.0001 - 0.001%.

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7. Composition as claimed in any of Claims 1 to 6, for use thereof in the treatment of oral halitosis.
8. Use of the composition claimed in any of Claims 1 to 6 for obtaining a mouth rinse for the treatment of oral halitosis.
- 5 9. Use of the composition claimed in any of Claims 1 to 6 for obtaining a toothpaste for the treatment of oral halitosis.
10. Use of the composition claimed in any of Claims 1 to 6 for obtaining a dental powder for the treatment of oral halitosis.
- 10 11. Use of the composition claimed in any of Claims 1 to 6 for obtaining a dental chewing gum for the treatment of oral halitosis.

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## EUROPEAN SEARCH REPORT

Application Number

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DOCUMENTS CONSIDERED TO BE RELEVANT									
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			TECHNICAL FIELDS SEARCHED (Int.Cl.6)						
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<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 33%;">Place of search</th> <th style="width: 33%;">Date of completion of the search</th> <th style="width: 34%;">Examiner</th> </tr> <tr> <td>MUNICH</td> <td>6 November 2002</td> <td>Sala-Jung, N</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	MUNICH	6 November 2002	Sala-Jung, N
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MUNICH	6 November 2002	Sala-Jung, N							
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone      Y : particularly relevant if combined with another document of the same category      A : technological background      O : non-written disclosure      P : intermediate document</p> <p>T : theory or principle underlying the invention      E : earlier patent document, but published on, or after the filing date      D : document cited in the application      L : document cited for other reasons      &amp; : member of the same patent family, corresponding document</p>									

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